

Therapy for Lysosomal Storage Disorders: a Matter for Stem Cells

Editorial

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The therapeutic potential of stem cells is based on their own physiological activity on maintain the tissue homeostasis. Thank to the asymmetric division stem cells generate one stem cell that remain within the niche and one progenitor cell that entries to a differentiation program and in turn repopulate the tissue where they reside [1-2]. Noteworthy, stem cells preserve this regenerative property even after their transplantation in a host damaged tissue because of they recognize the host microenvironment and start to activate a tissue repairing program [1-4].

Thus, many diseases have been treated by stem cell replacement approaches with or without genethrapy combination in the cases of genetic disorders [3-6]. Of note, outcomes have been shown the potential of stem cells to reestablish cells tissue of different ontogenic origin indicating a cell reprogramming activity perhaps induced by the host tissue toward the implanted donor stem cells [1]. Therefore, bone marrow transplantation (BMT) of hematopoietic stem cells (HSCs) has been successful applied for the treatment of hematological diseases, but also for the therapy of nonhematopoietic diseases such as Lysosomal Storage Disorders (LSDs) [5,7-8].

LSDs are a group of genetic diseases caused by deficiency of related lysosomal enzymes or cofactors as consequence of mutation in a deputed gene [9-10]. Lysosomal enzymes are involved on the degradation of the most biomacromolecules as well as on the production of intermediate compounds crucial for several cell functions [5-6,8-9]. Absence of such enzymes/cofactors produces accumulation of undegraded substrates and thereby cell dysfunctions and death of patients at pediatric age in the most severe forms of LSDs [5-6,8-9]. Therapy for LSDs generally consists

on supportive care. Effort has been made by nonconventional approaches ranging from enzyme replacement therapy to stem cell replacement therapy with or without gene therapy combination [5,7]. Benefits emerge by a recent work by Naphade S. and coworkers, demonstrating the capability of HSCs to restore the cystinosis, a multisystemic LSD, caused by a defective cystinosis (CTNS gene), a cystine lysosomal membrane transporter [11]. Successful outcomes are by stem cell treatment for the inherited Metachromatic Leukodystrophy (MLD), LSDs with neurological involvement caused by deficiency of the enzyme arylsulfatase A (ARSA) [8]. In this clinical trial, after BMT of adult HSCs engineered with lentiviral vector expressing the ARSA gene, all three presymptomatic MLD patients showed widespread, robust and stable ARSA gene replacement and high enzyme expression in the hematopoietic lineages and in cerebrospinal fluid. Most important the treatment prevented the manifestation of the disease and for the first time demonstrated that BMT of engineered HSCs could be capable to cure neurodegenerative disorders [8]. For these results this approach is considered a breakthrough compared to previous conventional BMT treatments [12,13]. LSDs takes advantage also by the therapeutic potential of other type of stem cells. This is the case of the Globoid cell leukodystrophy (GLD) a neurodegenerative LSDs caused by the deficiency of galactocerebrosidase (GALC) where adult bone marrow mesenchymal stem cells (BMSCs) transplantation into the animal model of the disease, improved motor function, twitching symptoms, weight and decreased inflammatory cell, globoid cell, and apoptotic cell levels in the sciatic nerves compared to untreated mice [14]. Similarly, GLD takes benefit by intracerebral neonatal transplantation of neural stem cells (NSCs) that provides functional GALC enzyme and ameliorates the functional impairment in endogenous subventricular zone (SVZ) cells which seems to be involved on maintaining a functional post-natal SVZ neurogenic niche [15].

Stem cells allow generating a disease model *in vitro*. In the case of LSDs, stem cell modeling led to elucidate pathophysiology mechanisms of these diseases and in turn to develop more proficient therapeutic approaches. For instance, alteration of self-renewal and proliferation of NSCs and impairment of neurons and oligodendrocytes survival is consequence of absence of GALC enzyme activity. Therefore insights into the mechanisms regulating the expression of GALC in NSCs from GALC could improve the understanding of GLD pathology [15]. Moreover, NSCs from the LSDs Tay-Sachs and Sandhoff (GM2-gangliosidosis) animal models and their differentiated progenies recapitulated hexosaminidase activity, isoenzyme composition, gene expression and ganglioside metabolism observed during embryonic and postnatal brain development in GM2 gangliosidosis and allowed the eluci-

dation of the events linking the accumulation of undegraded substrates as cosenquence of hexosaminidase activity deficiency [16].

In summary, the overall reports highlight the suitability of stem cells for the treatment of LSD but also for providing an in vitro model that, recapitulating the disease characteristics, allow the elucidation of the altered metabolic pathways. Thus, the therapy for LSD is a matter for stem cells.

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